2005 MAR 2 PCT/JP2003/12509

DRAWINGS

Figure 1

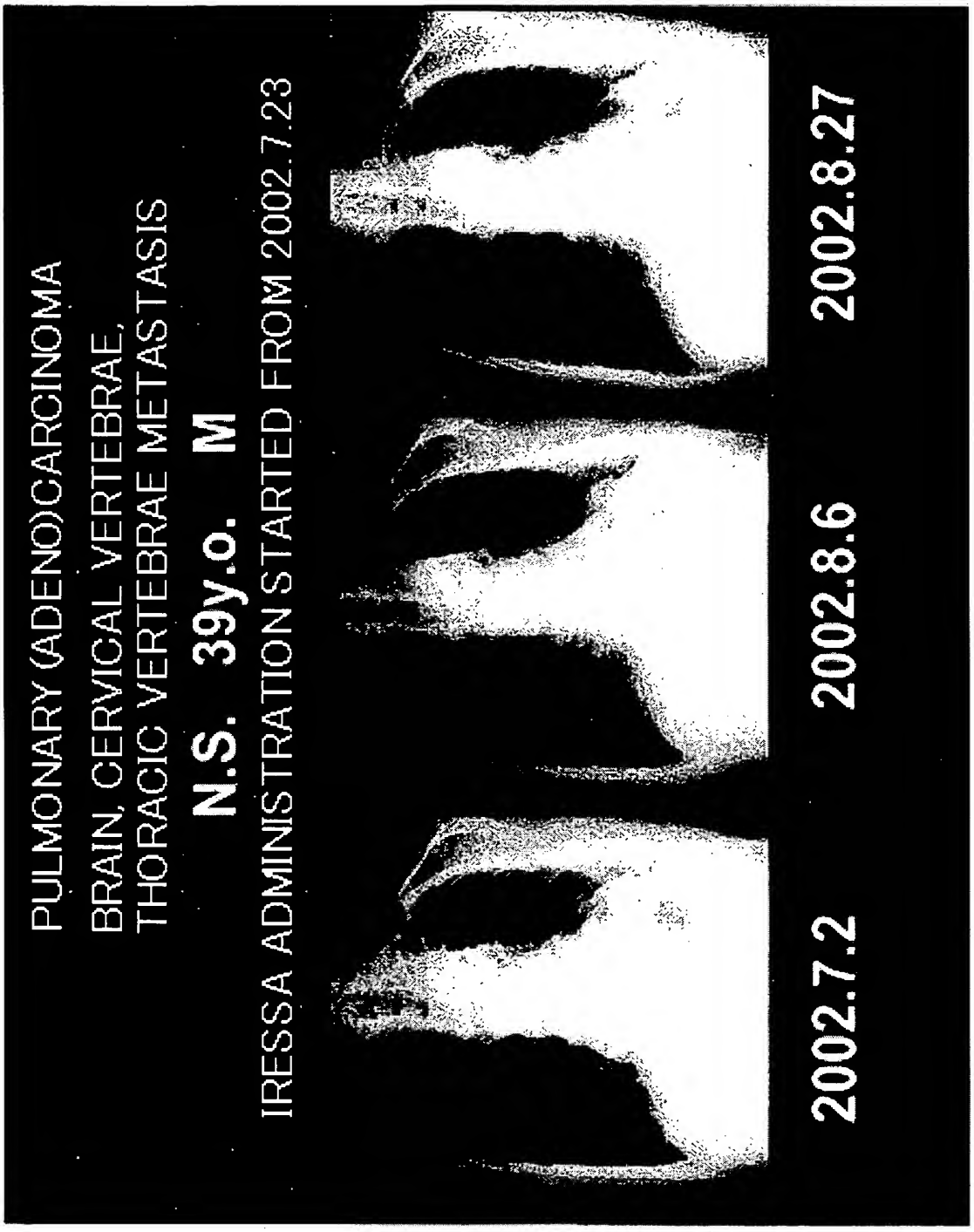

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Figure 2

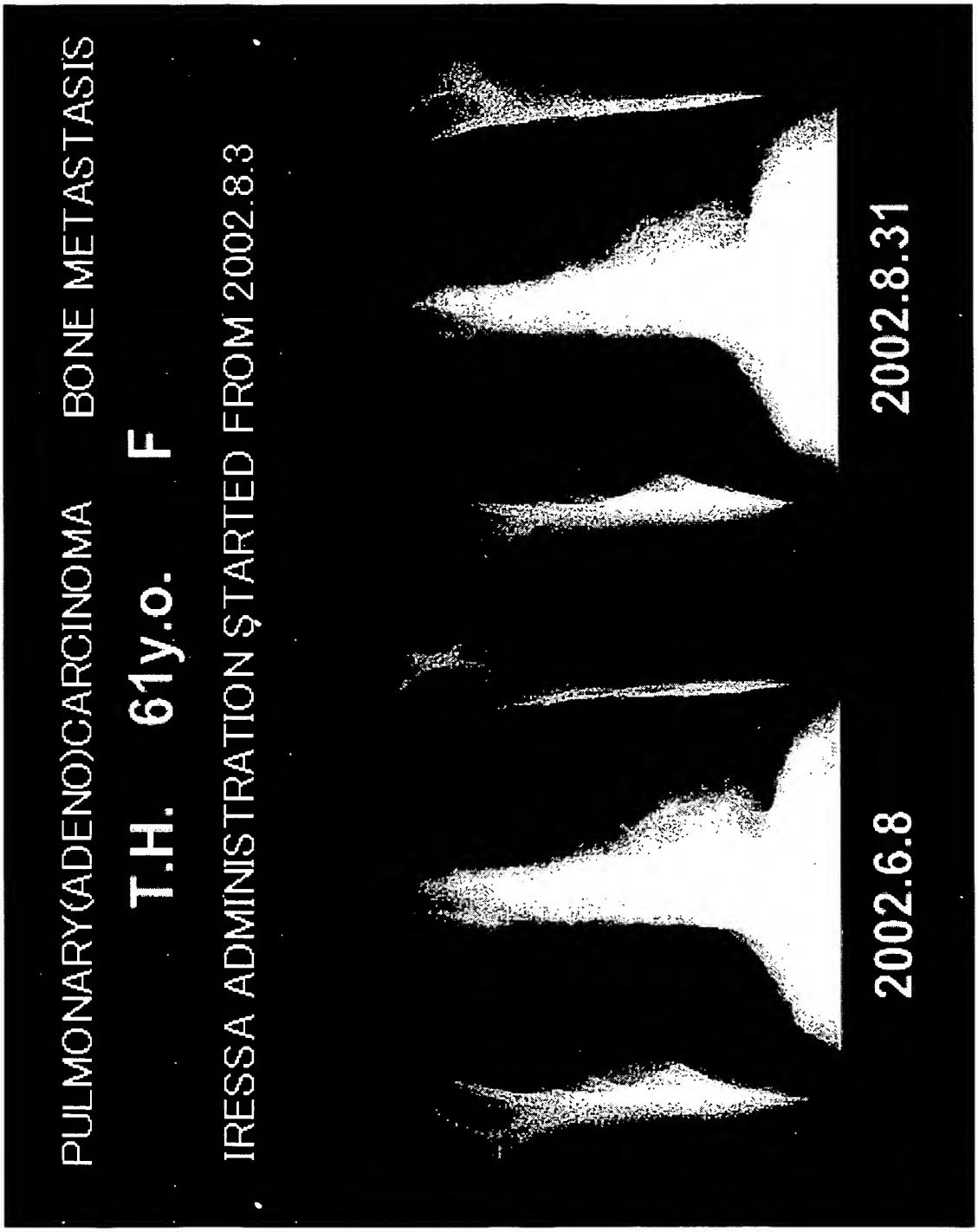

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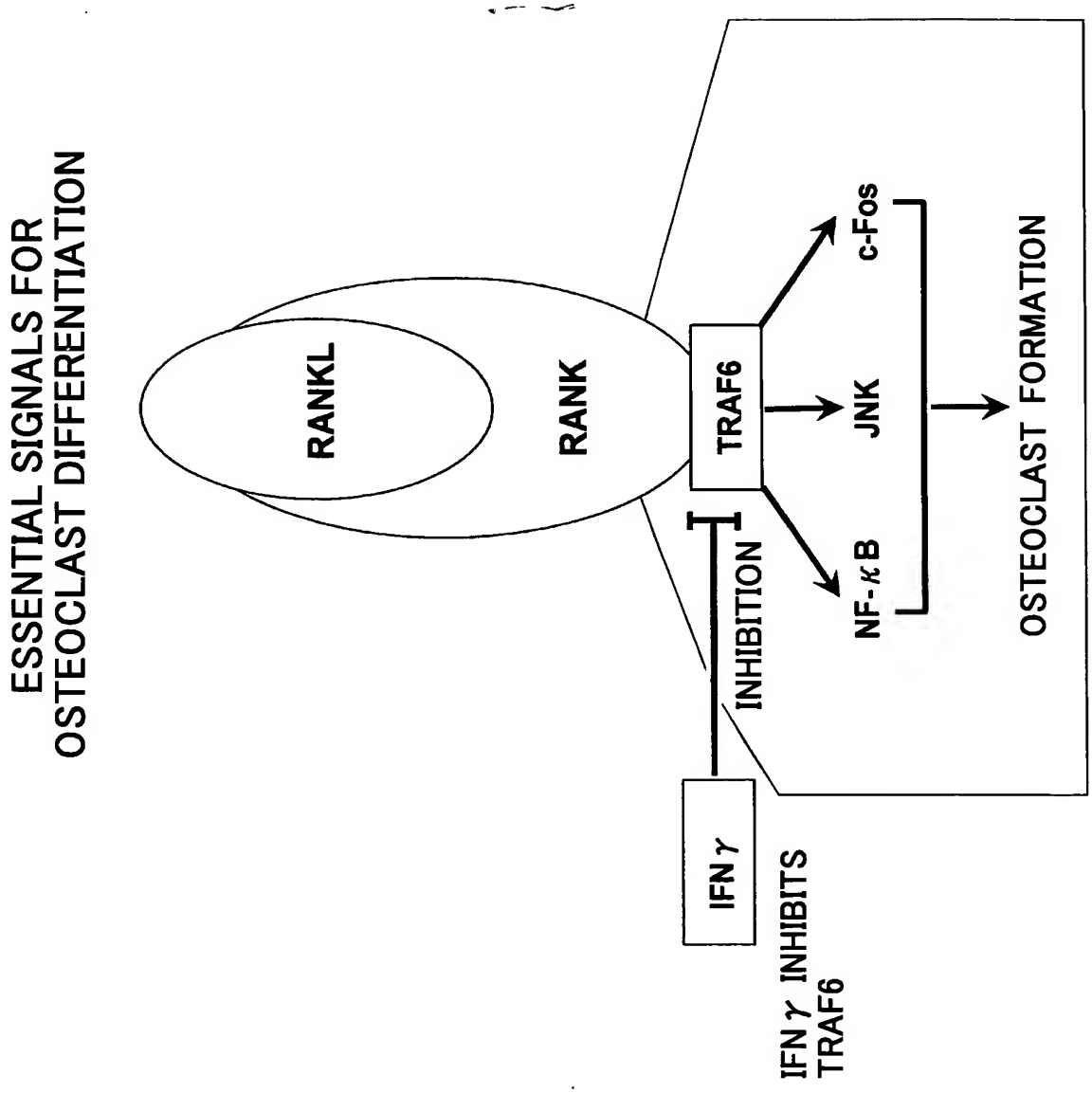
Figure 3



PCT/JP2003/012509 10.09.2003 PROS NAM S.L.

Figure 4

EFFECTIVE CASES FOR PULMONARY ADENOCARCINOMA
(COMBINED THERAPY OF IRESSA AND NITC)

		AGE	GEN-DER	METASTATIC FOCUS	RATING
1	T.H.	61	F	PLEURAPOPHYSIS	PR
2	N.S.	39	M	BRAIN, CERVICAL VERTEB-RAE, THORACIC VERTEBRAE	PR
3	H.T.	78	M		PR~CR
4	F.T.	66	F		PR
5	M.F.	51	F		PR
6	C.I.	59	M	BOTH LUNGS, BONE (MULTIPLE)	PR
7	S.Y.	69	M		PR
8	K.F.	71	F	BONE (MULTIPLE)	PR
9	K.M.	74	F		PR
10	T.S.	66	F		PR
11	O.K.	69	F		PR
12	U.S.	79	F	INTRAPULMONARY	PR
13	I.Y.	71	M	BONE (MULTIPLE)	NC~PR
14	I.Y.	73	M		NC~PR
15	O.K.	57	F		NC

RATE OF EFFICACY FOR PULMONARY ADENOCARCINOMA : PR 12/15(80.0%)
: NC 3/15(20.0%)

Figure 5

EFFECTIVE CASES FOR CANCER OF THE LARGE INTESTINE (COMBINED THERAPY OF IRESSA AND NITC)

COLON CANCER

		AGE	GEN-DER	SITE	METASTATIC FOCUS	RAT-ING
1	K.Y.	57	F	C		PR
2	S.I.	63	F	S	CERVICAL LYMPH NODE	PR
3	M.K.	53	M	A	CERVICAL LYMPH NODE, LUNG	PR
4	H.M	51	M	D	LIVER	PR
5	H.S.	64	F	S	LIVER, BONE	PR
6	S.N.	67	F	T	LUNG	NC
7	O.T	63	M	S+C	LUNG, LIVER	PD

CANCER OF THE RECTUM

		AGE	GEN-DER		METASTA-TIC FOCUS	RAT-ING
1	Y.Y.	57	M		LIVER	PR
2	O.T.	64	M	(RECTUM+A)		PR
3	K.H.	60	M			PR
4	K.M.	64	F		LUNG, LIVER	PR

RATE OF EFFICACY FOR CANCER OF THE COLON : PR 5/7(71.4%)
: NC 1/7(14.3%)
: PD 1/7(14.3%)

RATE OF EFFICACY FOR CANCER OF THE RECTUM : PR 4/4(100%)

RATE OF EFFICACY FOR CANCER OF THE LARGE INTESTINE : PR 9/11(81.8%)
: NC 1/11(9.1%)
: PD 1/11(9.1%)

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Figure 6

EFFECTIVE CASES OF COMBINED TREATMENT WITH IRESSA AND NITC

	PR	NC	PD	TOTAL n NUMBER
PULMONARY (ADENO) CARCINOMA	12(80.0%)	3(20.0%)	0 (0%)	15
CANCER OF THE LARGE INTESTINE	9(81.8%)	1(9.1%)	1(9.1%)	11
COLON CANCER	5(71.4%)	1(14.3%)	1(14.3%)	7
CANCER OF THE RECTUM	4(100%)			4
ANAL CANCER	1 (50%)		1 (50%)	2
RENAL CANCER	2(100%)			2
LINGUAL CANCER	1(100%)			1
BREAST CANCER	1(16.7%)	1(16.7%)	4(66.7%)	6
GASTRIC CANCER	1(33.3%)		2(66.7%)	3
PROSTATIC CANCER		2(100%)		2
ESOPHAGEAL CANCER		2(66.7%)	1(33.3%)	3
PANCREATIC CANCER		1(100%)		1
PHARYNGEAL CANCER		1(100%)		1
PAROTID CANCER		1(100%)		1
BLADDER CANCER			2(100%)	2
CERVICAL CANCER			1(100%)	1
OVARIAN CANCER	2(50.0%)	1(25.0%)	1(25.0%)	4
TOTAL	29(52.7%)	13(23.6%)	13(23.6%)	55

Figure 7

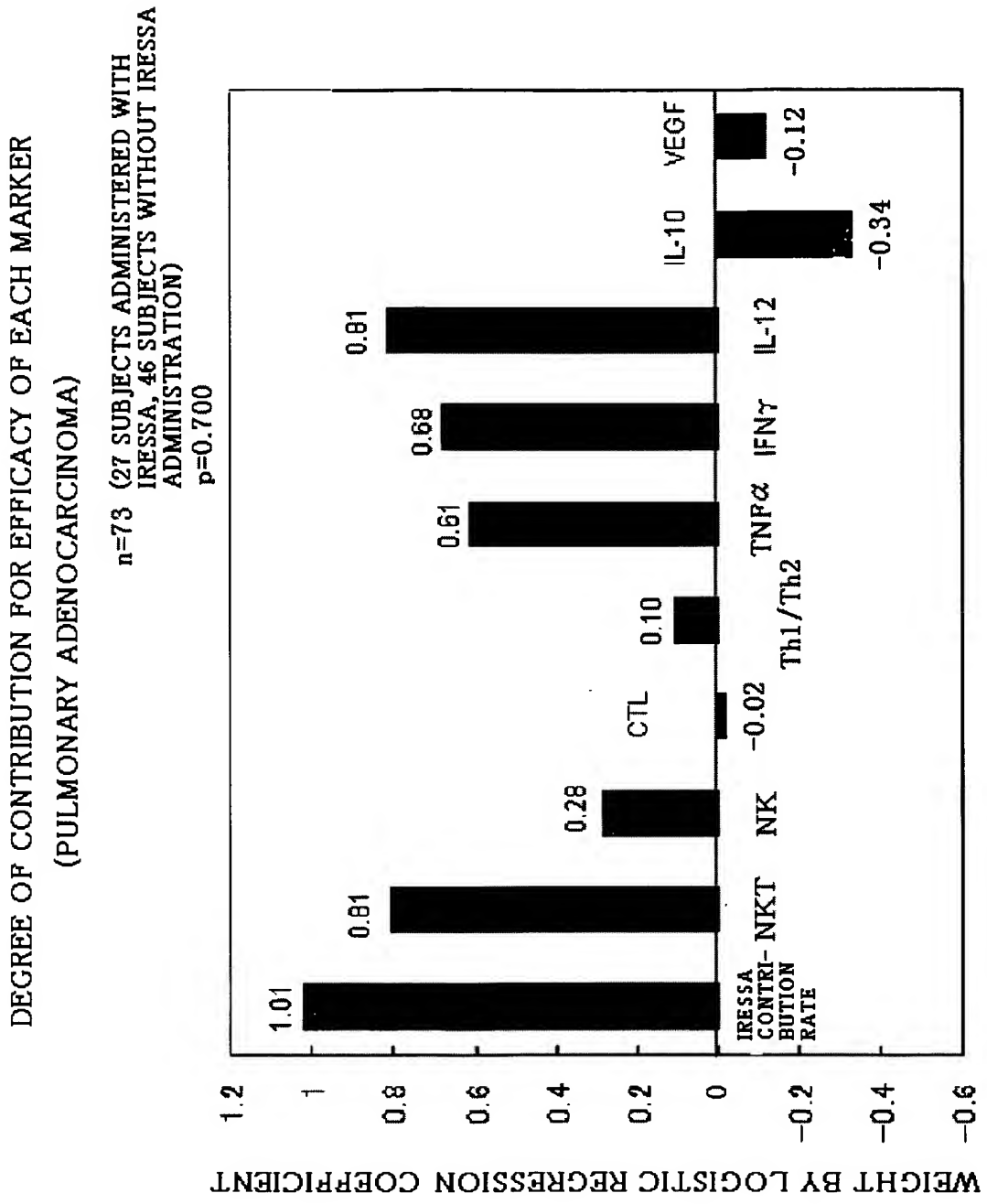
DEGREE OF CONTRIBUTION FOR EFFICACY OF EACH MARKER
(PULMONARY ADENOCARCINOMA)
n=73 (27 SUBJECTS ADMINISTERED WITH IRESSA, 46 SUBJECTS WITHOUT IRESSA ADMINISTRATION)
p=0.700
WEIGHT BY LOGISTIC REGRESSION COEFFICIENT
1.2
1
0.8
0.6
0.4
0.2
0
−0.2
−0.4
−0.6
IRESSA CONTRI-BUTION RATE
1.01
NKT
0.81
NK
0.28
CTL
−0.02
Th1/Th2
0.10
TNFα
0.61
IFNγ
0.68
IL-12
0.81
IL-10
−0.34
VEGF
−0.12

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Figure 8

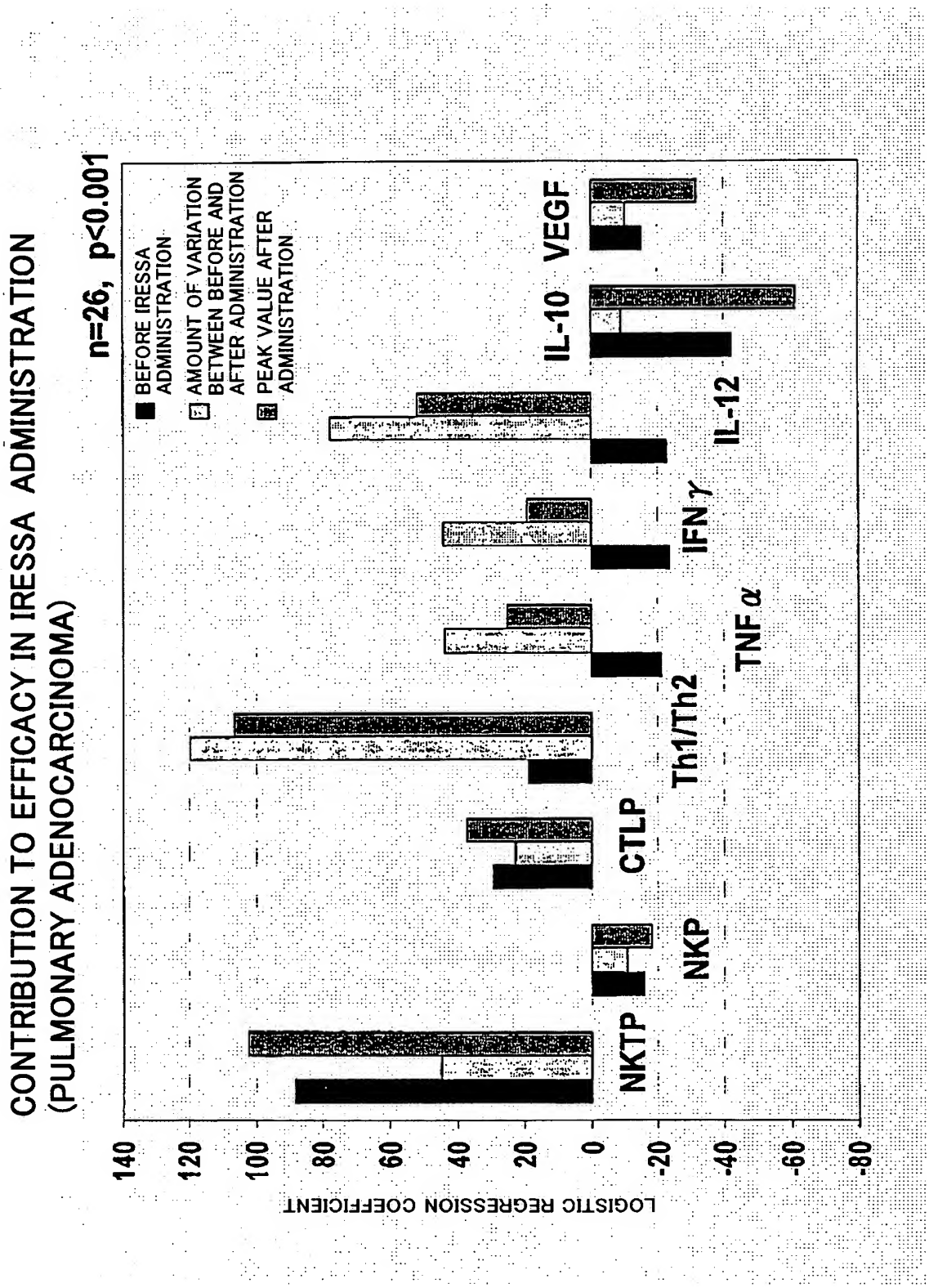

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Figure 9

COMPARISON OF EFFECTIVE CASES (B GROUP) AND INEFFECTIVE CASES (A GROUP) PRIOR TO IRESSA ADMINISTRATION

NKT PERFORIN ACTIVITY (%) BEFORE IRESSA ADMINISTRATION	EFFECTIVE CASES	INEFFECTIVE CASES	TOTAL
5.0 OR MORE	13	1	14
LESS THAN 5.0	8	6	14
TOTAL	21	7	28

(p<0.05)

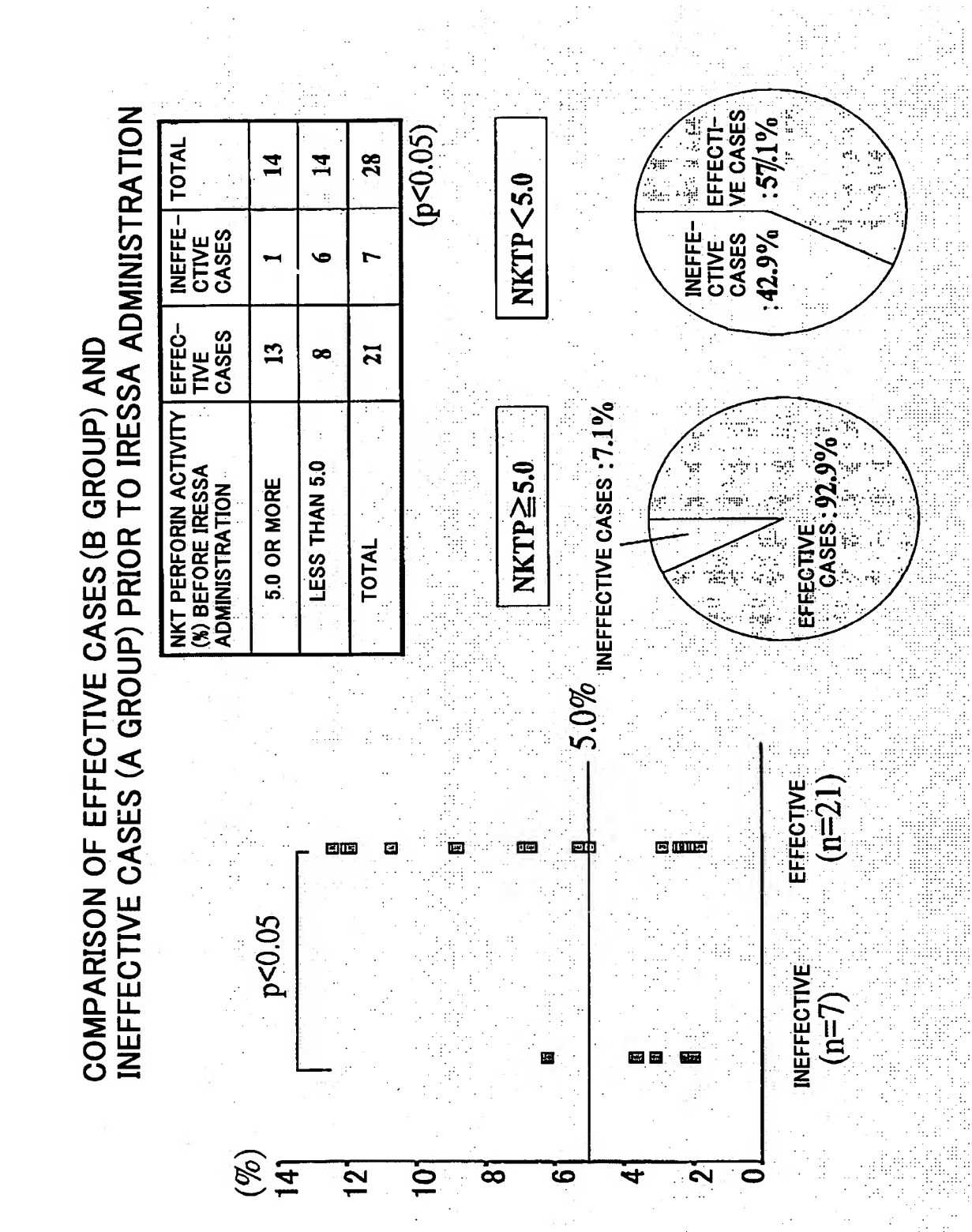

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Figure 10

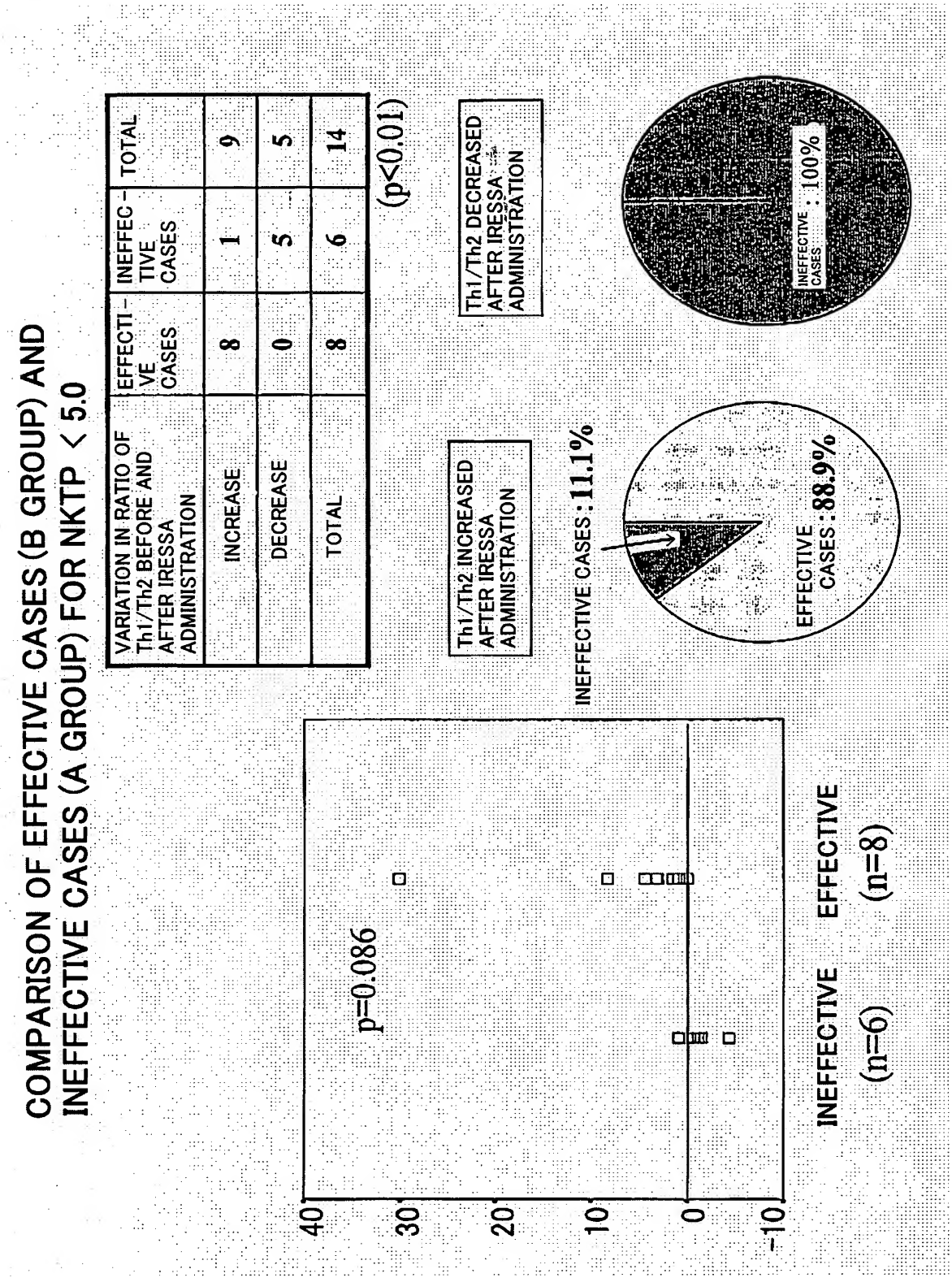


Figure 11

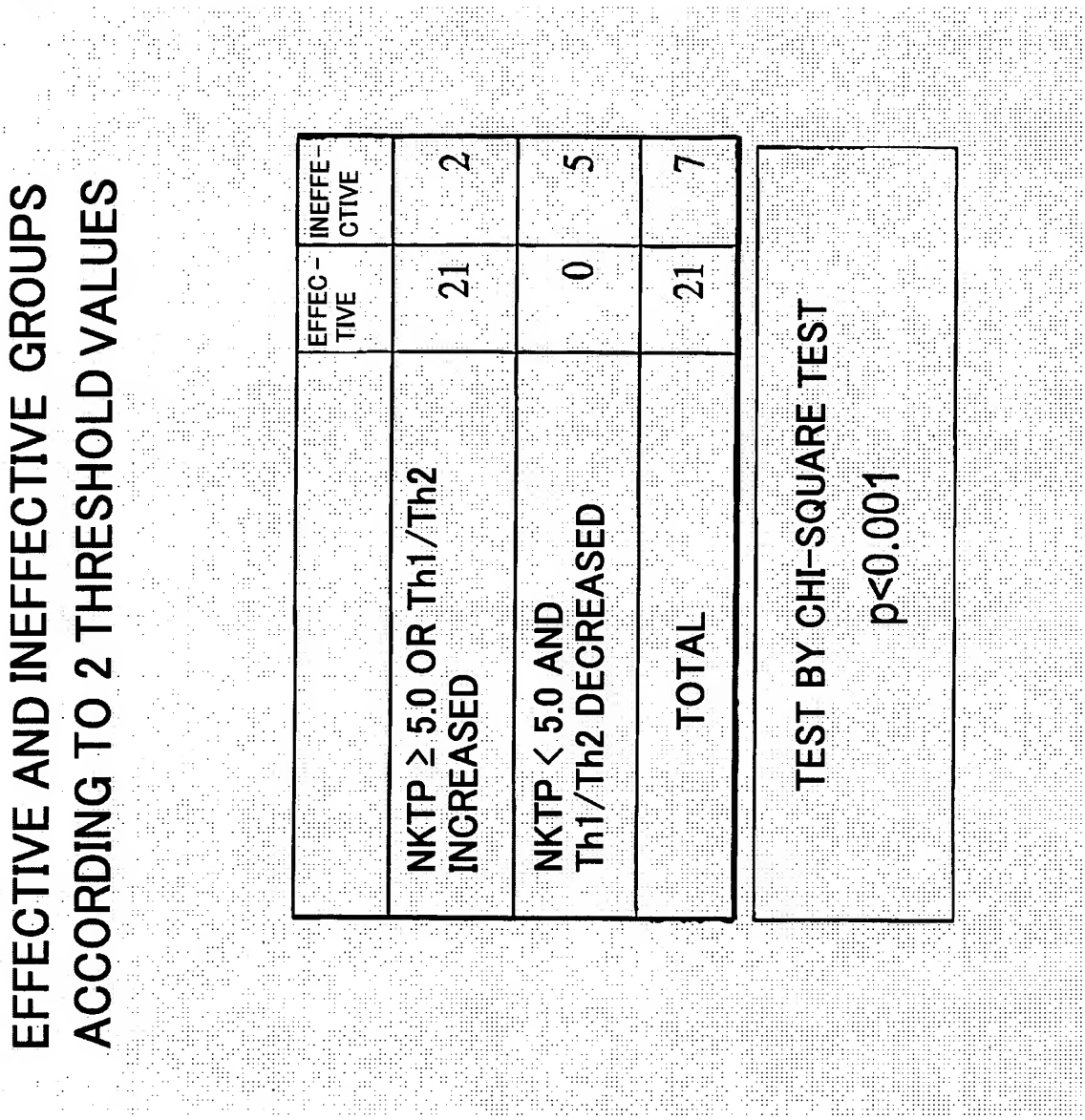

EFFECTIVE AND INEFFECTIVE GROUPS
ACCORDING TO 2 THRESHOLD VALUES
EFFEC-TIVE
INEFFE-CTIVE
NKTP ≥ 5.0 OR Th1/Th2 INCREASED
21
2
NKTP < 5.0 AND Th1/Th2 DECREASED
0
5
TOTAL
21
7
TEST BY CHI-SQUARE TEST
p<0.001

Figure 12

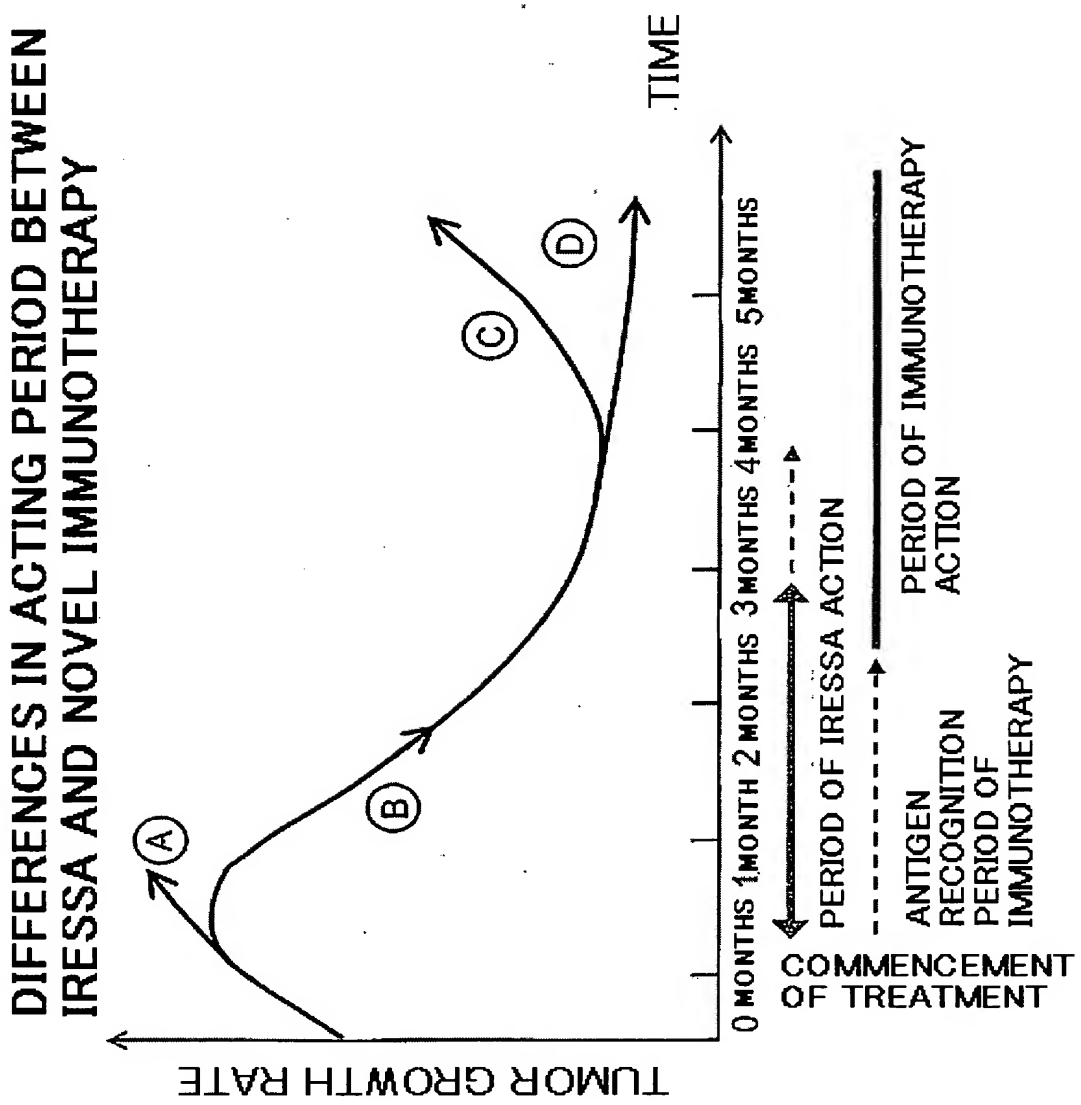

DIFFERENCES IN ACTING PERIOD BETWEEN IRESSA AND NOVEL IMMUNOTHERAPY
TUMOR GROWTH RATE
TIME
A
B
C
D
0 MONTHS 1 MONTH 2 MONTHS 3 MONTHS 4 MONTHS 5 MONTHS
PERIOD OF IRESSA ACTION
PERIOD OF IMMUNOTHERAPY ACTION
ANTIGEN RECOGNITION PERIOD OF IMMUNOTHERAPY
COMMENCEMENT OF TREATMENT

Figure 13

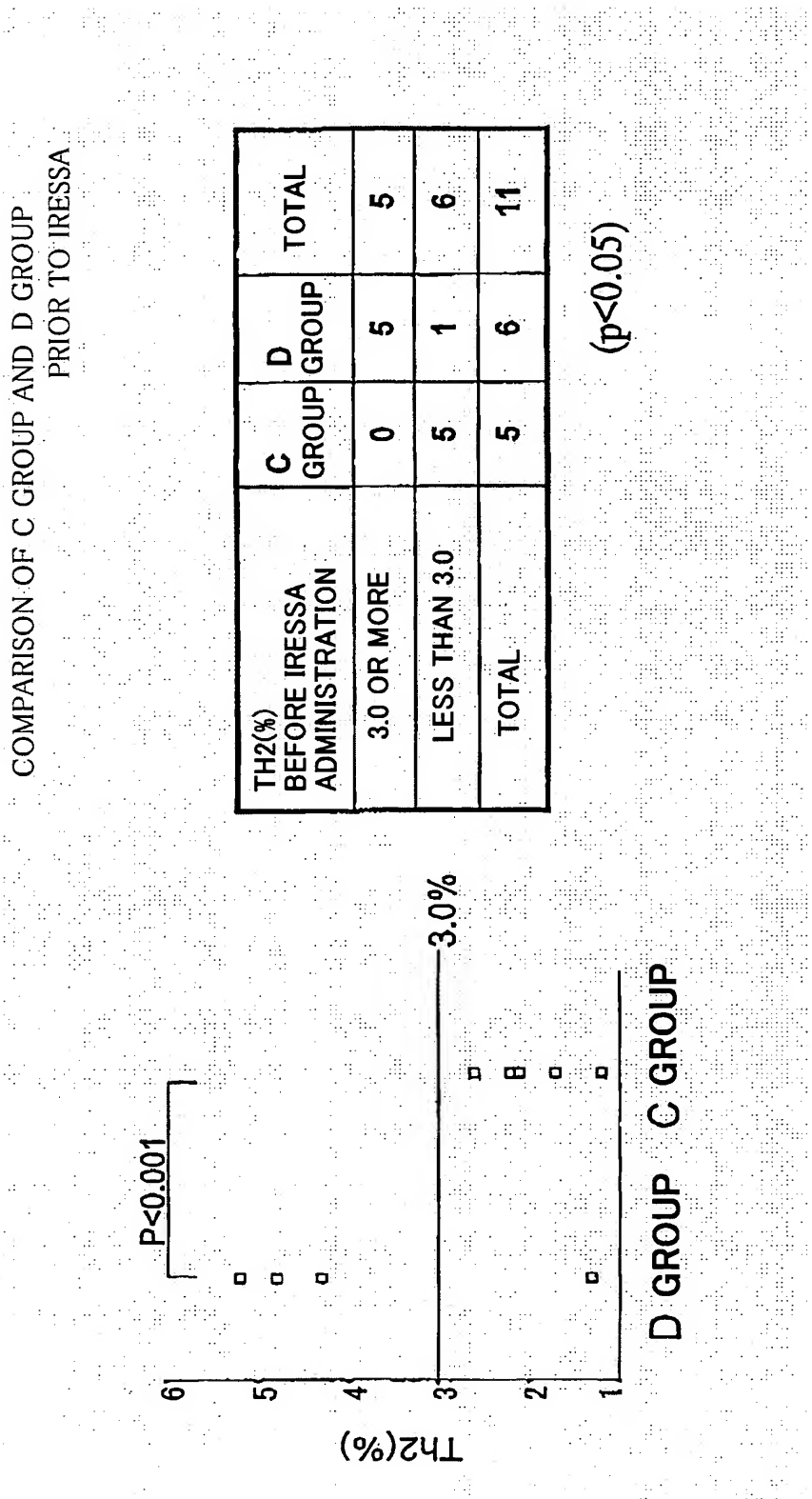

COMPARISON OF C GROUP AND D GROUP
PRIOR TO IRESSA
TH2(%) BEFORE IRESSA ADMINISTRATION
C GROUP
D GROUP
TOTAL
3.0 OR MORE
0
5
5
LESS THAN 3.0
5
1
6
TOTAL
5
6
11
(p<0.05)
P<0.001
3.0%
TH2(%)
6
5
4
3
2
1
D GROUP
C GROUP

Figure 14

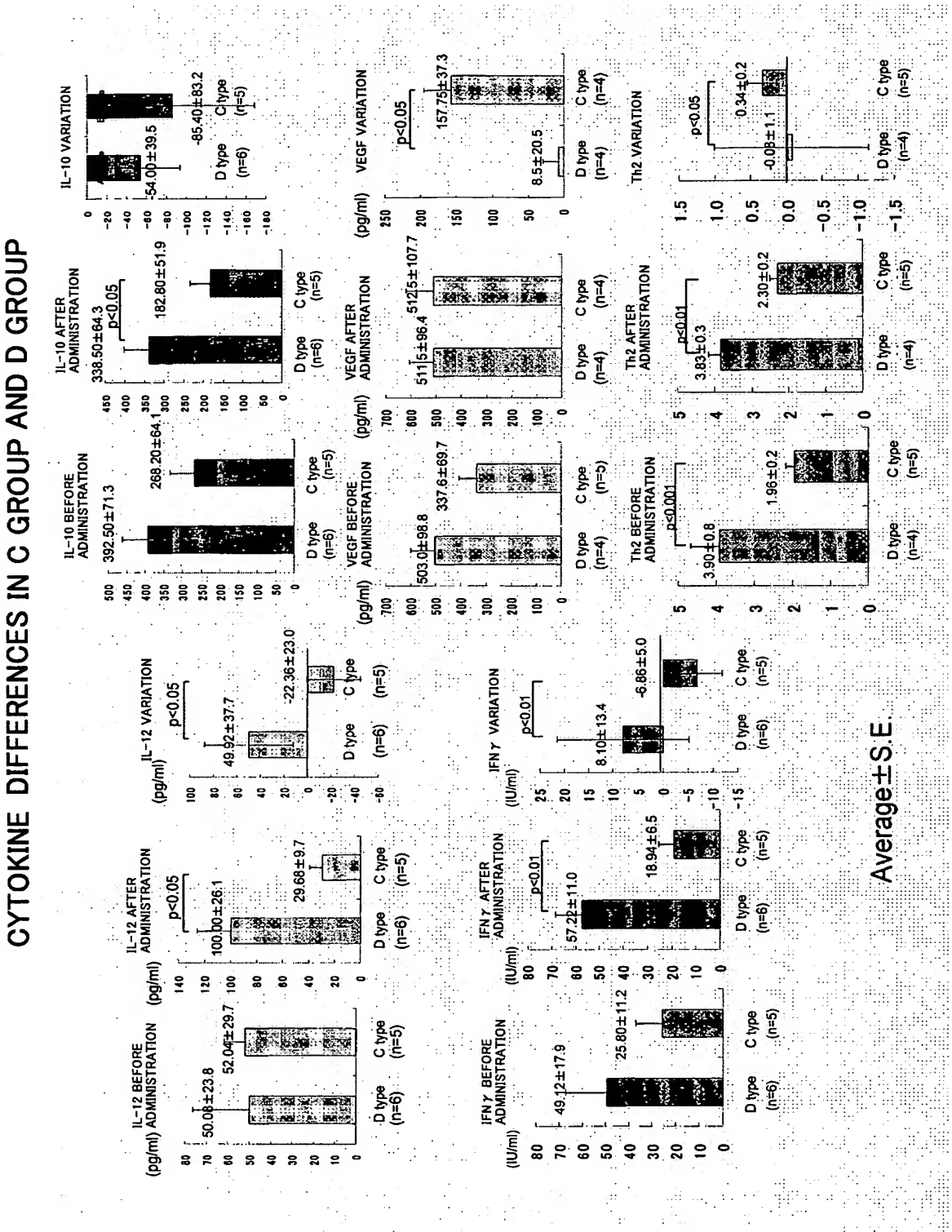
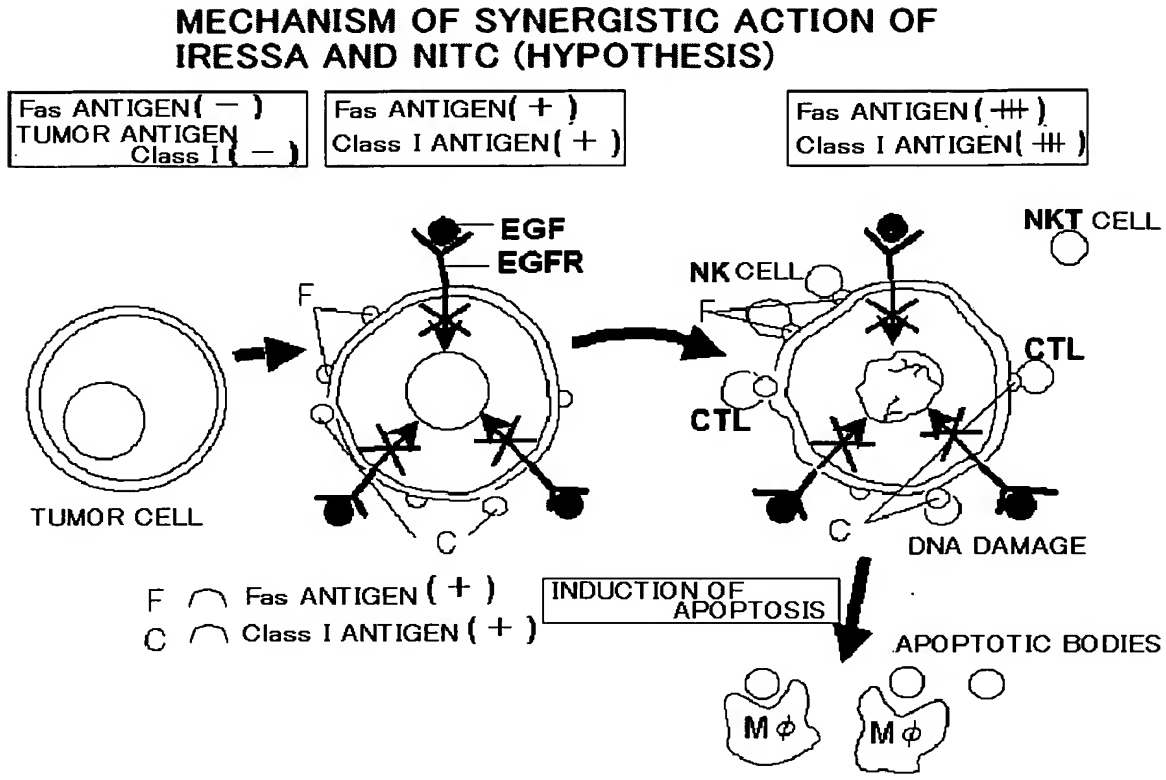

CYTOKINE DIFFERENCES IN C GROUP AND D GROUP
IL-10 VARIATION
IL-10 AFTER ADMINISTRATION
IL-10 BEFORE ADMINISTRATION
VEGF VARIATION
VEGF AFTER ADMINISTRATION
VEGF BEFORE ADMINISTRATION
IL-12 VARIATION
IL-12 AFTER ADMINISTRATION
IL-12 BEFORE ADMINISTRATION
Th2 VARIATION
Th2 AFTER ADMINISTRATION
Th2 BEFORE ADMINISTRATION
IFNγ VARIATION
IFNγ AFTER ADMINISTRATION
IFNγ BEFORE ADMINISTRATION
D type (n=6)
C type (n=5)
D type (n=4)
C type (n=4)
p<0.05
p<0.01
p<0.001
Average±S.E.

Figure 15


MECHANISM OF SYNERGISTIC ACTION OF IRESSA AND NITC (HYPOTHESIS)
Fas ANTIGEN(−)
TUMOR ANTIGEN Class I(−)
Fas ANTIGEN(+)
Class I ANTIGEN(+)
Fas ANTIGEN(++)
Class I ANTIGEN(++)
EGF
EGFR
F
C
TUMOR CELL
NK CELL
NKT CELL
CTL
CTL
DNA DAMAGE
F Fas ANTIGEN (+)
C Class I ANTIGEN (+)
INDUCTION OF APOPTOSIS
APOPTOTIC BODIES
Mφ
Mφ

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